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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/594,162

09/26/2006

Pierre Bartsch

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EXAMINER

MAIER, LEIGH C

ART UNIT

PAPER NUMBER

1623

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DELIVERY MODE

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/594,162	<b>Applicant(s)</b> BARTSCH ET AL.	
	<b>Examiner</b> Leigh C. Maier	<b>Art Unit</b> 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-10 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-10 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. ____.                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/20/07, 10/29/08</u> .                                       | 6) <input type="checkbox"/> Other: ____.                          |

## DETAILED ACTION

### *Claim Objections*

Claim 1 comprises a chemical structure designated “formula (I).” However, the structure, as drawn is chemically nonsensical. For the purposes of examination, the formula is being construed as being the trioxypyrimidine formula described at paragraph [0026]. It is the opinion of the examiner that this is a reasonable construction because the species recited in claim 3 and 10, claims depending from claim 1, are consistent with this trioxypyrimidine formula.

Applicant is directed to correct this structure in a manner consistent with the formula described in the specification.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grams et al (US 6,242,455) in view of Csabai et al (Int. J. Pharm., 1993).

The construction of the instant claims is discussed above. Further regarding the structural formula set forth in the claims and specification, it is noted that the two nitrogens in the pyrimidine-trione ring do not have a third substituent shown. It is the opinion of the examiner that one of ordinary skill would understand this to be a typographical error omitting the hydrogens. There is no discussion of other substituents at these positions, and all the species are compounds having unsubstituted nitrogens at these ring positions.

Grams teaches the instant trioxypyrimidine compounds and describes them as barbituric acid derivatives. See col 2-3 and col 8, lines 17-37. The reference further teaches the preparation of pharmaceutical compositions of these compounds for administration in liquid or solid form, further comprising additives, such as solubilizers. See col 7, beginning line 58 and continuing through col 8, line 11. The reference does not teach the compound as a cyclodextrin complex.

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Csabai teaches the preparation of inclusion complexes comprising hydroxylpropyl- $\beta$ -cyclodextrin and several trioxypyrimidines—barbituric acid compounds—structurally similar to the instant compounds. See Table I. This type of inclusion formation leads to modified physico-chemical properties of the complexed compound, such as enhanced solubility and bioavailability. See 1<sup>st</sup> paragraph of the reference.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a pharmaceutical composition comprising a trioxypyrimidine compound disclosed by Grams and any typical excipient as suggested by the reference. It would be further obvious to prepare the compound as an inclusion complex with cyclodextrin for the solubilizing effect that accompanies complexation. One of ordinary skill would be motivated with a reasonable expectation of success because Grams had suggested the use of solubilizers, and Csabai had taught that very similar compounds form complexes with cyclodextrins.

Claims 1-5, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grams et al (US 6,242,455) in view of Csabai et al (Int. J. Pharm., 1993) and further in view of Mura et al (Int. J. Pharm., 2003) and Piel et al (J. Pharm. Sci., 1997).

Grams and Csabai teach as set forth above. The references do not teach the addition of L-lysine or L-arginine as an adjuvant.

Mura teaches that the addition of auxiliary ingredients, such as arginine or lysine, to a drug:HP- $\beta$ -cyclodextrin complex increases the overall solubility of the drug. See section I and Table 1. The discussion in section I indicates that this is a general phenomenon and not limited to the drug disclosed in Mura. See also Piel at abstract and Discussion.

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It would have been obvious to one having ordinary skill in the art at the time the invention was known to prepare a cyclodextrin inclusion complex of the compounds disclosed by Grams, as discussed above. It would be further obvious to add an auxiliary component, such as lysine or arginine, for the additional solubilizing benefits. The use of such components is known for the preparation of ternary complexes that lead to increased solubility of the active ingredient. It would be within the scope of the artisan to arrive at the optimum additive through routine experimentation.

Claims 1 and 3-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grams et al (US 6,242,455) in view of Csabai et al (Int. J. Pharm., 1993) and further in view of Szente et al (Adv. Drug Deliv. Rev., 1999).

Grams and Csabai teach as set forth above. The references do not teach the full scope of cyclodextrins recited in the claims.

Szente discusses the use of highly soluble cyclodextrins, such as randomly methylated, sulfoalkyl and hydroxypropyl, as pharmaceutical excipients. See, particularly, section 1 and 2.2.

It would have been obvious to one having ordinary skill in the art at the time the invention was known to prepare a cyclodextrin inclusion complex of the compounds disclosed by Grams, as discussed above. It would be further obvious to use any cyclodextrin known to have utility in the preparation of pharmaceutical products, such as those discussed by Szente, with a reasonable expectation of success.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claims because the examined application claim is either anticipated by, or would have been obvious over, the reference claims. See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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Claims 1-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2 and 3 of copending Application No. 10/594,101. Claim 2 is rejected further in view of Mura et al (Int. J. Pharm., 2003) and Piel et al (J. Pharm. Sci., 1997).

Although the conflicting claims are not identical, they are not patentably distinct from each other. The reference claims are drawn to a therapeutic method of using a cyclodextrin complex of a trioxypyrimidine compound. In carrying out the recited method, it is obvious to prepare the instantly recited complex. The reference claims do not recite particular cyclodextrins as set forth in the instant claims. However, the specification defines "water-soluble" cyclodextrins as the same ones that are recited in the instant claims. It would be obvious to one having ordinary skill at the time the invention was made to select any cyclodextrin defined in the specification as being a water soluble one. It would be further obvious to prepare the inclusion complex with an additional excipient for the administration to a subject as directed by the reference claims.

With respect to claim 2, the reference claims do not recite the addition of L-lysine or L-arginine.

Mura and Piel teach as set forth above.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the product used in the reference claims by the addition of an auxiliary component, such as arginine or lysine, that is known to enhance the solubility of a drug that is complexed with a cyclodextrin with a reasonable expectation of success.



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This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

*Examiner's hours, phone & fax numbers*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Thursday, and Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Anna Jiang (571) 272-0627, may be contacted. The fax number for Group 1600, Art Unit 1623 is (571) 273-8300.

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/Leigh C. Maier/  
Primary Examiner, Art Unit 1623  
January 2, 2009